DISCUSSION

With entry of this amendment, the claims pending for prosecution are claims 1-16, 25-26, 29-47, 53-57, 60 and 64-65. Claims 17-24, 27-28, 48-52 and 61-63 are withdrawn from consideration pursuant to the Requirement for Restriction originally made on May 12, 2003 and memorialized in the current office action. Claims 58 and 59 are cancelled. Claim 65 is newly added.

The first line of the specification is amended to reflect applicants' claim for priority from U.S. Provisional Application Nos. 60/263,315, filed on January 22, 2001 and 60/326,807, filed October 3, 2001. The Abstract is amended to include formula I. Claim 16 is amended to include R^4. Claim 37 is amended to include H. Thus, claims 38-40 now properly depend from claim 37. Claim 45 is amended to correct the spelling of "alkyl." Claim 46 is corrected to add a hyphen inadvertently omitted from the compound name. Claim 47 is amended to delete the first-named compound. Claim 53 is amended to include a definition of R^5. Claim 60 is amended to depend from claim 1. Claim 65 is added to claim the first named compound that was deleted from claim 37, said compound being one wherein R^3 and R^4 do form a ring. 47

These amendments presented herein are not believed to present new subject matter.

The Restriction Requirement

The Patent Office has restricted the claims into five groups, as identified on pages 2-3 of the Office Action. Applicants traverse the restriction as between Groups I and II inasmuch as it is improper for the PTO to issue intra-claim restrictions. As is required by PTO practice, however, applicants affirm their election of Group I , claims 1-16, 25-26, 29-47, 53-60 and 64 wherein the substituents R^3 and R^4 do not form a ring, for continued prosecution in this application. Applicants' election of Group I does not indicate applicants' agreement with the propriety of the restriction requirement. Applicants' reserve the right to pursue the non-elected subject matter in one or more divisional applications.

The Section 112 Rejections

Claims 1-16, 25, 26, 30, 31, 33, 37-41, 43, 45, and 53-60 stand rejected under 35 USC §112, second paragraph, as being indefinite. Specifically, it is asserted that the recitation of a "pharmaceutically acceptable ester" in the claims is of unclear scope. This rejection is traversed.

In the support of its rejection, the Patent Office gives little weight to applicants' exemplification at page 12 of the instant application of what is a "pharmaceutically acceptable ester" and further asserts that "there is no guidance as to what other sites can be esterified and what types of esters." The basis of this rejection is entirely inconsistent with established Patent Office practice and applicable law.

The various substituent groups that may be successfully employed while retaining the beneficial utility of applicants' core structure are fully elaborated in the instant specification, which contains 129 examples inclusive of results of bio-pharmaceutical assays. The Patent Office has not challenged the patentability, including proper support and claiming, of the pharmaceutically active acid derivatives. However, in an entirely inconsistent approach, the Patent Office has challenged as violative of 35 USC §112, the additional elaboration of the disclosed and claimed invention as including "...the pharmaceutically acceptable ...esters." As mentioned above, this ground of rejection is irreconcilable with the wisdom in the relevant field of art, and contravenes both controlling legal and United States Patent & Trademark Office precedent.

When a search is made in the LEXPAT library of the LEXIS legal database for claims which contain the limitation "pharmaceutically acceptable w/2 esters" the search is broken off with the warning from LEXIS that over 1,000 responsive patents have been found. When the search was limited to just the decade of the 90's, the results found 720 patents employing the term. Were the instant rejection to be upheld, it would without question be tantamount to announcing the retroactive invalidation of the generic claims of hundreds if not thousands of US pharmaceutical patents. No valid reason in either law or science is advanced on the present record for doing so.

The reason that such terminology is frequently found in claims of pharmaceutical patents is self evident to the skilled worker in the pharmaceutical arts. When the claimed compounds include organic acids, it is considered conventional to also claim the pharmaceutically acceptable salt and ester forms of the acid derivatives inasmuch

as it is well recognized in the art that such forms will dissociate to provide the active free acid principle *in vivo*. *See, e.g.*, US Patent No. 5,965,741 issued to Zeneca Ltd.: "An in vivo hydrolysable ester of a compound of formula (I) containing carboxy group is, for example, a pharmaceutically acceptable ester which is hydrolysed in the human or animal body to produce the parent acid...." (Column 8 at lines 36-39). The '741 patent goes on to claim in unlimited fashion the salts, esters and amides of what is an already large and complicated genus of aromatic ether compounds.

The '741 patent and its use of pharmaceutically acceptable ester language is in no way exceptional, as the LEXIS numbers attest, as the formation of an ester from the free carboxyl group is commonplace chemistry involving one of the most robust and easily practiced classes of reactions. As set forth in US Patent No. 5,616,600, issued to Sankyo Company Ltd.: "There is no particular limitation upon the nature of the alcoholic moiety of the ester, provided that, where it is intended for therapeutic use, it is 'pharmaceutically acceptable', which, as is well-known to those skilled in the art, means that it does not, or does not to an unacceptable extent, reduce the activity of the compound or increase its toxicity and all esters conventionally formed for compounds of this type may be formed with the compounds of the invention." (Column 8, line 66 to column 9, line 6).

See also US Patent No. 5,731,299 issued to Procter & Gamble: "The term 'pharmaceutically-acceptable salts and esters' as used herein, means hydrolyzable esters and salts of the phosphosulfonate compounds which have the same general pharmacological properties as the acid form from which they are derived, and which are acceptable from a toxicity viewpoint." (Column 40, lines 27-32). Although the '299

patent does disclose and exemplify a few preferred salts, it does not bother to provide such disclosure as to esters, which are nevertheless claimed. It clearly, as in many other pharmaceutical patents, had no need to provide such disclosure or teachings given the knowledge of the skilled worker in this art.

In contrast to the above patents, applicants have disclosed certain preferred ester groups and typical esterification reactions for preparing esters of the core compounds of formula I (see e.g. paragraphs 92-94 and 347). No scientific evidence or reasoning is advanced by the Patent Office to question the apparent recognition in the prior art and patent literature that Applicants' "pharmaceutically acceptable esters" would be as readily understood and accessible in the full scope claimed.

Together with applicant's disclosure, e.g. 92-94 and 347, a skilled artisan would certainly understand and envision which groups and sites may properly be esterified in applicants' core structure in formula I. That is all the law requires for definiteness. It is well settled that the specification need not teach or disclose in detail that which is well known in the art. In re Meyers 161 USPQ 668 (CCPA 1969); General Electric Co. v. Brenner 159 USPQ 335 (App. DC 1968).

The Patent Office's statement at page 5 that "[m]any different compounds can result from the derivitization to such different types of esters...." evidences that the Patent Office used an incorrect standard in lodging this rejection. All that §112, second paragraph, requires is that the meaning of the term can be ascertained by one skilled in the art. The fact that there may be many such esters is irrelevant to the definiteness

requirement. "...[B]readth is not to be equated with indefiniteness, as we have said many times." In re Miller 169 USPQ 597, 600 (CCPA 1971).

As long as one skilled in the art knows what the claims cover, the term is not indefinite. *See*, Ex parte Altermatt, 183 USPQ 436, 437 (Pat. Off. Bd. of App. 1974). As evidenced by the knowledge expressed in the prior art exemplified by the above cited examples from the patent literature, the meaning and scope of the recital of "pharmaceutically acceptable esters" is well-known to the skilled worker and thus satisfies §112, second paragraph. No reasoning or evidence to the contrary has been provided by the Patent Office. This Section 112, second paragraph, rejection is legally and technically improper and should be withdrawn.

Certain unidentified claims (applicants' presume the same claims as identified in the above Section 112 rejection) are also rejected as not being clearly defined in that the rings formed by NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ allegedly are not clearly defined. This rejection is also traversed. Applicants have defined these substituents in a manner clearly understood by a skilled artisan.

Contrary to what appears to be the Patent Office's expectation as stated on page 6 of the Office Action, applicants do not have to specifically identify each and every atom in the possible rings that can be formed by the groups NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$. Such a requirement would be tantamount to requiring the specific chemical formula for every ring contemplated by a genus. Clearly that is not the current state of the law. Applicants may claim a genus of compounds without identifying each compound within the genus. Analogously, applicants my describe and claim a genera

of rings by describing the rings without identifying each such ring. Thus, applicants' description that each of the groups NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ can form a ring having 5-6 atoms, which may include one or more "additional heteroatoms," is clearly understood by one skilled in the art to convey that the "N" is part of the ring, not "adjacent" or "non-adjacent" to it and that such ring may include additional heteroatoms. Applicants submit that this definition is fully descriptive of the rings contemplated, for Example, for $NR^{12}R^{13}$ as option for R^4, as shown in Examples 26-28,50,55,58,59, 61,62,64,65 and many others, and no more is required. Applicants do not have state whether the rings are saturated or unsaturated. Both are contemplated, and well understood to be, within the term "ring."

Applicants disagree with the Patent Office's contention that the only guidance for the above ring systems is provided on page 18. Guidance is provided throughout the application, including the 129 Examples, as mentioned above.

Moreover, applicants' definition of the groups NR^7R^8, $NR^{12}R^{13}$ and $NR^{15}R^{16}$ as optionally forming a ring is well-recognized in the pharmaceutical arts. *See* for example US Pat. No. 6,197,804, No. 6,313,143, No. 6,313,310, and No. 6,440,959. For an even broader example, *see* US Patent No. 5,731,299.

This Section 112, second paragraph, rejection is also legally and technically improper and should be withdrawn.

Claims 1-16, 25-26, 30-31, 33, 37, 41, 43, 45, 53 and 56-60 are rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. Specifically, the Patent Office

asserts that it is not reasonable to expect that "the myriad of compounds embraced by the claims will all share the same physiological properties," that is, antiproliferative activity. Office Action at p.7. The basis for the rejection is contrary to established legal precedent and the rejection is thus traversed.

Applicants submit that the claims are fully enabled in view of the extensive and detailed specification. 35 U.S.C. § 112, first paragraph, requires that the specification enable a person skilled in the art to which the invention pertains to make and use the invention. There is no basis on the current record to infer, as the Patent Office has done, that one skilled in the art would have any problem ascertaining which compounds within applicants' defined genus would have antiproliferative activity. On the contrary, applicants' Example 125 succinctly shows how to test for antiproliferative activity. This is all the law requires for applicants to claim the invention broadly.

The Patent Office's apparent contention that all compounds embraced by the claims must have the claimed utility for the instant application to be enabled is contrary to legal precedent. It is hornbook law that claims must be interpreted in a reasonable manner and should not be read to include possibly inoperative species. *See, e.g.,* In re Angstadt, 190 USPQ 214, 219 (CCPA 1976); Ex parte Breuer, 1 USPQ2d 1906 (Bd. Pat. Int. App. 1986); and In re Smythe, 178 USPQ 279 (CCPA 1973). The Court's admonitions in In re Smythe are particularly on point. In Smythe the court rejected the Board's premise that the use of the term "inert fluids" makes the claim so broad as to include inoperable fluids. The court stated:

> [I]t is almost always possible to so construe a claim as to have it read on inoperative embodiments....We therefore cannot agree with the board that the rejection under the first paragraph of § 112 is any more sustainable because the broader term "fluid" includes some "liquids" which might not work. *Id* at 286.

Those compounds within applicants' genera that may not have antiproliferative activity are easily discerned using the disclosed assay of Example 125 (or any of a number of similar art-recognized assays) without undue experimentation. That is all that the enablement requirement of Section 112 requires. *See* Atlas Powder Co. v. E.I. Dupont de Nemours & Co., 224 USPQ 409 (Fed. Cir. 1984).

The cases cited by the Office in support of the enablement rejection are inapposite and/or distinguishable. Unlike In re Fisher , 166 USPQ 18 (CCPA 1970), the instant application is not concerned with purified hormone compositions having limitations to polypeptide content and specific units of activity. Moreover, in Fisher, the CCPA found that "appellant has not enabled the preparation of ACTHs having" certain potencies. *Id* at 24. Thus, the patent applicant in Fisher did not sufficiently teach how to make the claimed invention, which is readily distinguishable from the pending rejection which is based on an alleged failure of "how to use" the claimed invention.

In re Surrey, 151 USPQ 724 (CCPA 1966) is also factually distinguishable. The breadth of the claims and the number of examples in the Surrey application are totally different from applicants' specification. Moreover, and more importantly, a linchpin of the holding in In re Surrey was the Court's finding that "no unequivocal statement in appellant's specification or in his brief here that compounds other than those actually

tested are anticonvulsants or psychomotor stimulants. Appellant simply says that the '*physical embodiments*' of his invention 'have been tested***and found to possess' the named properties."(emphasis original). *Id.* at 730. In contrast, applicants' clearly assert that the compounds claimed have antiproliferative properties, not just those compounds that were tested. *See, e.g.*, paragraphs [0002], [0025], [0026], etc., of the instant application.

In view of applicants' explicit assertion of utility, the burden is on the Patent Office to present credible scientific evidence supporting its statements that applicants' claimed compounds do not have the stated utility. Mere doubt, without specific scientific evidence or reasons, which is all the current Office Action contains, is not sufficient for maintaining a rejection under 25 USC § 112, first paragraph. In re Marzocchi, 169 USPQ 367 (CCPA 1971), is directly on point. In reversing a rejection under 25 USC § 112, first paragraph, similar to the one pending in the instant application based on the PTO's assertion that the breadth of the claimed terms cover inoperable embodiments, the CCPA held:

> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *Id.* At 370.

In fact, in In re Fouche, 169 USPQ 429 (CCPA 1971), cited by the Patent Office in support of this rejection, there appears to have been evidence in the record presented by applicants (namely affidavits) that cast doubt on whether certain claimed

compounds would have the stated utility. No such evidence exists on the current record. Thus, no basis exists for requiring applicants to provide reasonable assurances that all compounds will be useful for the described utility. On the contrary, as the CCPA stated in In re Armbruster, 185 USPQ 152 (CCPA 1975):

> Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct. *Id.* at 153.

The Patent Office cites to Grant et al., Drug Resistance, ***6:15-26*** (2003), as evidencing that CDK inhibitors are not known as a broad-based anti-tumor agents for treating man. Applicants' are not asserting that all CDK inhibitors are broad-based anti-tumor agents. If they were, then applicants' lives (and those of all pharmaceutical chemists) would truly be much easier! Applicants have presented evidence at pages 3-7 of their application that quite a number of pharmaceutical companies have found small molecules that inhibit CDKs and are investigating their potential as clinically useful anti-tumor agents. Also, applicants are asserting that *their* specific CDK inhibitors are useful antitumor agents. Furthermore, the utility of certain CDK inhibitors as anti-tumor agents is supported by the fact that at least three such compounds are currently in clinical trials. *See, e.g.,* P. M. Fischer and A. Gianella-Borradori, "CDK inhibitors in clinical development for the treatment of cancer," Expert Opin. Investig. Drugs, ***12(6):955-970*** (2003) (a copy of which is enclosed for the Examiner's convenience). Finally, the PTO's own guidelines clearly state that clinical utility before the FDA is the not the proper measure of enablement. *In vitro* testing is adequate.

This enablement rejection is thus legally unfounded and factually incorrect and should be withdrawn.

Method claims 58-60 are additionally rejected as not being enabled inasmuch as they refer to the treatment of cancer generally. Claims 58 and 59 are cancelled. Claim 60 is amended to refer specifically only to breast, colon, lung and prostate cancer. This rejection is thus overcome and should be withdrawn.

The Section 103 Rejection

Claims 1-16, 25, 26, 29-36, 38, 41-46, 53-60 and 64 are rejected under 35 USC § 103(a) as being unpatentable over WO 99/21845 ("Chong"). This rejection is traversed.

The R^2 substituent of Chong is very broad and does include substituted and unsubstituted rings, including phenyl. *See, e.g.* page 6. However, on page 10 of the Chong application, he is very explicit that when R^2 is cyclic, the location of the substituent on the ring does matter. Note, for example, the statement on lines 4-5, page 10, "even more preferably, R^2 is such a cyclic ring structure bearing a substituent at the position adjacent or vicinal to the point of attachment (to the core structure)." In lines 6-15, he further states that ortho-substituted aromatic rings are preferred. The only substituted aromatic rings disclosed for R^2 on pages 10-11 all include at least one ortho substituent. Claim 1 of Chong specifically limits R^2 to a "ring structure having a substituent at the position adjacent to the point of attachment" (page 162, lines 17-18). More significantly, however, the enzyme data reported in Table I, pages 133- 151, of

Chong demonstrate the criticality of having ortho substitution when R^2 is a ring, particularly phenyl. Note, for example, on page 138 the difference in potency between compound C(17) which is ortho substituted (Ki=72 nM) and compound C(18) which is essentially the same as C(17) but is para substituted (Ki=12,900 nM). The ortho substitution yielded a compound that is 179 times more active in the reported enzyme assay than the para substituted compound.

At page 10 of the Office Action the Patent Office asserts that structural isomers are expected to have the same activity. As shown above, this assertion is not in fact consistent with what Chong teaches about his compounds. On the contrary, Chong teaches that when R^2 is a substituted ring, proximity of the substituent to the point of attachment to the rest of the structure yields better activity. Chong shows that ortho substitution is best, and meta is better than para (*see, e.g.* page 133, compound D(1) which is meta substituted, has a potency of Ki= 490 nM, while the para substituted compound D(2) has a potency of Ki= 5000nM).

In direct contrast to Chong's teachings, applicants found that their compounds lacking ortho substitution are not only highly active, but unexpectedly, are also highly selective. *See* applicants' specification paragraph [0024]. Applicants' compounds are thus not taught or suggested by Chong.

A reference must be considered in its entirety, including any portions that teach away from a claimed invention. *See* Bausch & Lomb v. Barnes-Hind/Hydrocurve, Inc., 230 USPQ 416, 420 (Fed. Cir. 1986). While Chong broadly discloses substituted rings,

of which phenyl is an option, for his R^2 substituent, a skilled artisan reading Chong would not be motivated to make applicants' compounds not bearing ortho substitution as these compounds would be expected to have undesirably low activities. Thus, for the reasons provided above, Chong actually teaches away from applicants' meta- and para-substituted compounds.

A final point of distinction is that there is no suggestion in Chong that his compounds, like applicants', are Cdk4 inhibitors that are also selective against other Cdks. The selectivity of applicants' compounds is shown in Table I, pages 140-143. Thus, in summary, applicants' compounds possess unexpected properties over Chong's disclosed compounds and are patentable over Chong.

In view of the foregoing, the Section 103 rejection is traversed and should be withdrawn.

The Patent Office queries applicants' proviso excluding R^4 being Cl when R^3 is $-NO_2$. Applicants' are asked whether this was due to prior art as the Patent Office has not found any art describing such compounds. Applicants' concur with Patent Office that these compounds are novel. Applicants' inclusion of this proviso was not due to prior art references, but rather the activity/selectivity of the compounds.

Informalities

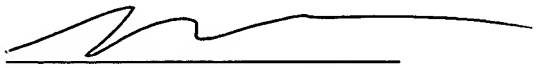
At page 10 of the Office Action applicants are informed that the Examiner did not receive publications C1 and C2 submitted with applicants' Information Disclosure

Statement dated March 7, 2002. These publications are again submitted herewith. Please note that C2 is a conference handout of a presentation that was given at a Gordon Conference. Also, applicants are informed that the Examiner apparently did not receive the front page of the Supplemental Information Disclosure Statement submitted by applicants on July 1, 2002. A copy of the entire July 1 submission is again resubmitted herewith.

CONCLUSION

In view of the foregoing amendments and remarks, applicants' submit that the instant application is in condition for allowance and solicit early action to that end.

Respectfully submitted,



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